REMARKS/ARGUMENTS

Applicants are grateful for the thoroughness of the examination and appreciate the opportunity to demonstrate that Applicants had possession of the invention which was fully enabling prior to the time of application. Claims 1-21 are pending in the subject application and are currently under consideration. Currently, claims 1-21 stand rejected under 35 U.S.C. § 112, first paragraph under the written description and enablement requirements. Claims 1-13 and 15 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Remarks Directed to the Rejection of Claims 1-21

under 35 U.S.C. § 112, First Paragraph, Written Description:

Withdrawal of the rejection of claims 1-21 is respectfully requested for at least the following reasons. The specification of the subject application describes the invention in its entirety such that a person having ordinary skill in the art would recognize that Applicants had possession of the invention as of the filing date.

Possession may be demonstrated by describing an actual reduction to practice, showing drawings, or by describing distinguishing identifying characteristics. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). There is a strong presumption that the application as filed contains an adequate written description. *Id.*

Independent claims 1, 14 and 21 have been amended to correct an error such that the ligand listed in the claims is Fas ligand. This amendment is being presented solely to correct an unintentional error that was unrelated to the patentability of the present claimed invention. Further, Applicants do not present this amendment as narrowing the scope of his claims and does not relinquish any equivalents known or unknown at the time of filing. This amendment

recognizes the statements in the specification that other known apoptosis ligands are similarly operative. This correction is fully supported by the specification *inter alia* at p. 6, line 20; p. 15, line 7; p. 20, line 7; p. 48, lines 11-18. Therefore the specification provides sufficient written description for Fas ligand.

An adequate written description of a DNA may be achieved by presentation of a precise definition, such as by structure, formula, chemical name, or physical properties sufficient to distinguish it from other materials. *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993). A person having ordinary skill in the art recognizes that the sequence of Fas ligand was published and available at NM 000043 (Human mRNA transcript 1) (also published was a cDNA at D38122) or NM007987 (mouse) and was knowledge in the art at the time the application was filed. As an additional example of a ligand, Fas associated death domain protein (FADD) was also available as a primary RNA and protein sequence at the time of filing. (Chinnaiyan, AM (1995) *Cell* 81: 505; Boldin, MP (1995); 270:7795; GeneBank Number X84709.)

Additionally, the subject application adequately provides a description of how and from what source Fas ligand nucleic acid sequence can be and has been obtained. Several sources for Fas ligand were known in the art at the time of filing and are incorporated in the subject application. These include that described in Example 2 (p. 30) as well as reference 45 (Zhang HG et al, *J. Virol.*, 72(3):2483-2490, 1998) incorporated by reference (p. 51). Further, Zhang et al fully describes the construction of a suitable vector with the capability of expressing Fas ligand. Example 2 similarly describes the incorporation of Fas ligand into a functional vector for use in the presently claimed methods. Figures 16 and 17 independently and in conjunction with Examples 34 and 35 describe construction of a suitable vector(s) for use in the present invention. Further, p. 16, lines 13-16 briefly describe the incorporation of the gene sequence of a ligand

gene such as that encoding Fas ligand into a vector. Therefore, adequate written description of Fas and numerous other apoptosis ligands, as well as modifications thereof, were known in the art at the time the subject application was filed, and a person having ordinary skill in the art recognizes that Applicants had possession of the invention at the time of filing.

As the mechanism of action of Fas ligand is adequately described in the present specification and was known in the art at the time the subject application was filed, sufficient written description for a second ligand that "induces apoptosis of said T-cell by the same mechanism as said Fas ligand" is present as well. The subject specification describes several other apoptosis ligands that are "similarly operative." (p. 15, line 8.) These illustratively include: "Fas ligand 2 which induces apoptosis by acting with death domain region molecules DR3, DR4 and DR5; TNF which induces apoptosis by acting with TNFRI; Granzyme B and porferin which are natural killing molecules associated with T-cells; and antibodies specific to T-cell apoptosis ligand receptors: anti-Fas, anti-DR3, anti-DR4, anti-DR5 and anti-TNFR1." (p. 15, lines 9-13.) Furthermore, it is recognized in the art that "a polynucleotide modification of Fas ligands to produce multimers of the Fas ligand is a means of increasing apoptosis potential of the Fas ligand." (p. 20, lines 11-13.) Thus, modifications of Fas ligand at the DNA, RNA, amino acid, post-translational modification, or other level produces apoptosis ligands that are similarly operative to Fas ligand and are examples of molecules suitable as said second ligand.

It is further recognized in the art that Fas ligand 2 represents the FADD (Fas Associated Death Domain) protein that similarly functions in association with Fas to induce apoptosis. (Chinnaiyan, AM (1995) *Cell* 81: 505; Boldin, MP (1995); 270:7795; NCBI accession number NM 000043.) The presence of Fas ligand and FADD in complex with Fas to induce apoptosis

identifies a common pathway by which FADD and Fas ligand function similarly such that FADD is a non-limiting example of a suitable said second ligand.

Further, as claims 2-13 depend from claim 1 and claims 15-20 depend from claim 14, each of these dependent claims incorporate by reference the novel limitations of the claims from which they refer. Applicants submit that additional bases exist for the patentability of the claims dependent from claims 1 and 14 and reserve the right to later make these of record.

Therefore, adequate written description of several examples of second apoptosis ligands that function similar to Fas ligand were knowledge in the art at the time the subject application was filed, and a person having ordinary skill in the art recognizes that Applicants had possession of the invention at the time of filing.

In light of the above remarks, withdrawal of the rejection claims 1-21 under 35 U.S.C. § 112, First Paragraph, Written Description is respectfully requested.

Remarks Directed to the Rejection of Claims 1-21

Under 35 U.S.C. § 112, First Paragraph, Enablement:

Withdrawal of the rejection of claims 1-21 under 35 U.S.C. § 112, First Paragraph, Enablement is respectfully requested for at least the following reasons. The claims contain subject matter that is described in the specification in such a way as to enable a person having ordinary skill in the art to which it pertains, or with which it is most clearly connected, to make and use the invention.

Independent claims 1, 14 and 21 have been amended to correct an error such that the ligand listed in the claims is Fas ligand. This amendment is being presented solely to correct an unintentional error that was unrelated to the patentability of the present claimed invention.

Further, Applicants do not present this amendment as narrowing the scope of his claims and does not relinquish any equivalents known or unknown at the time of filing. This amendment recognizes the statements in the specification that other known apoptosis ligands are similarly operative. This correction is fully supported by the specification *inter alia* at p. 6, line 20; p. 15, line 7; p. 20, line 7; p. 48, lines 11-18.

For the above mentioned reasons adequate description of Fas ligand is present in the subject specification to enable a person having ordinary skill in the art to make and use Fas ligand in the subject invention. The presence of nucleic acid sequences for Fas ligand, FADD, and other similarly operative apoptosis ligands is publicly available. Furthermore, techniques for construction of viral vectors or plasmids are well known in the art and are briefly described in the subject specification. (p. 16, lines 13-16; Example 2, p. 30.) As such it would not require undue experimentation to isolate or identify a nucleic acid molecule encoding Fas ligand for use in the claimed methods.

Similarly, example nucleic acid sequences for FADD (described above), TNF (M30964), Granzyme B (NM 004131; NM 138517), and porferin were known in the art at the time of filing. The construction and use of antibodies to Fas (Hayashi, H., *Apoptosis*, (1998) 3(6):431) and other targets operative in the present invention were similarly known in the art. Thus, a second vector expressing a second ligand that induces apoptosis of said T-cell by the same mechanism as said Fas ligand would not require undue experimentation for a person having ordinary skill in the art to identify or isolate.

Finally, the specification fully enables a person having ordinary skill in the art to make and use the claimed invention. Illustrative examples or terminology may be used to teach how to make and use the invention. *In re Vaeck*, 947 F.2d 488, 496 & n.23 (Fed. Cir. 1991). Numerous

non-limiting examples are provided in the subject specification demonstrating the subject invention. Figure 2 and Example 14 demonstrate the subject invention producing ligand levels capable of inducing apoptosis in A20 cells; Figure 3 further demonstrates this effect *in vivo*; Figures 4, 8, 10, 11 and 12 demonstrate *in vivo* induction of immunotolerance to adenovirus; Figures 13 and 15, as well as Example 5, demonstrate function of the present invention in specific target cells; Example 19 demonstrates decreased T-cell expansion in treated mice; Example 22 demonstrates in vitro and in vivo specific T-cell tolerance to antigens; Example 23 demonstrates induction of allogenic T-cell tolerance by Fas ligand expressing APCs in mice; and treatment of lung disease by the claimed methods are described in Examples 37 and 38.

Further, as claims 2-13 depend from claim 1 and claims 15-20 depend from claim 14, each of these dependent claims incorporate by reference the novel limitations of the claims from which they refer. Applicants submit that additional bases exist for the patentability of the claims dependent from claims 1 and 14 and reserve the right to later make these of record.

In sum, numerous examples of construction and use of the claimed invention both *in vitro* and *in vivo* are present in the subject specification. Therefore, enablement under 35 U.S.C. § 112, First Paragraph is satisfied.

In light of the above remarks, withdrawal of the rejection claims 1-21 under 35 U.S.C. § 112, First Paragraph, Enablement is respectfully requested.

Remarks Directed to the Rejection of Claims 1-13 and 15

Under 35 U.S.C. § 112, Second Paragraph:

Withdrawal of the rejection of claims 1-13 and 15 under 35 U.S.C. § 112, Second Paragraph, is respectfully requested for at least the following reasons. The claims particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Independent claim 1 has been amended to include the limitation "exposing said host to said transfected cell whereby immunotolerance to said vector is promoted." This limitation is fully supported by the specification (Examples 37 and 38.) Transfection of said cell may occur *in vitro* and *in vivo*, and subsequent exposure of the transfected cell to the host either by administration or by the presence of the transfected cell as a portion of the host results in promoting immunotolerance. Therefore, the preamble of the subject independent claim 1 is achieved by the method steps set forth in the claim.

Further, as claims 2-4 and 7-13 depend from claim 1, each of these dependent claims incorporate by reference the novel limitations of the claims from which they refer. Applicants submit that additional bases exist for the patentability of the claims dependent from claim 1 and reserve the right to later make these of record.

Claim 15 is definite as a depending on independent claim 14 that has been amended for the above mentioned reasons to include the limitation Fas ligand.

In light of the above amendments and remarks, withdrawal of the rejection of claims 1-13 and 15 under 35 U.S.C. § 112, Second Paragraph, is respectfully requested.

Remarks Directed to the Objection to Claim 10

as Objectionable Under 37 CFR 1.75:

Claim 9 has been cancelled so any potential objection to claim 10 as being a substantial duplicate thereof is moot.

SUMMARY

Claims 1-21 are currently pending in this application. Applicants submit that claims 1-21 are now in allowable form and directed to patentable subject matter. Reconsideration and allowance of the pending claims is solicited. Should the Examiner have any suggestions as to how to improve the form of the pending claims, he is respectfully requested to contact the undersigned attorney in charge of this application.

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Respectfully submitted,

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